#3

S/N 10/018719

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Becker, et al.	Docket No.:	13390.2USWO
Serial No.:	10/018719	Filed:	December 14, 2001
Int'l Appln No.:	PCTEP00005517	Int'l Filing Date:	June 15, 2000
Title:	USE OF GROWTH HORMONE (HGH) FOR THE TREATMENT OF SEXUAL FUNCTIONAL DISTURBANCES		

CERTIFICATE UNDER 37 CFR 1.10
'Express Mail' mailing label number: EV072823491
Date of Deposit: March 21, 2002
I hereby certify that this paper or fee is being deposited with the United States Postal Service 'Express Mail Post Office To Addressee' service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

By: Chris Stordahl

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, D. C. 20231

Dear Sir:

In connection with the above-identified application filed herewith, please enter the following preliminary amendment.

The present application was filed in the GERMAN language. Applicant now supplies the English translation of the application and the verified English translation of the specification are supplied herewith.

IN THE SPECIFICATION

Please amend the specification as follows:

Administration of Growth Hormone (hGH) for Therapy of Sexual Functional Disorders

Technical Field

[001] This invention concerns the introduction of human growth hormone (hGH, GH) for the manufacture of medicaments for the treatment of sexual functional disorders in both male and female patients as well as the specific methods of treatment undertaken.

Background of the Invention

[002] Symptoms indicating sexual functional disorders are, for example, lack or loss of libido, problems relating to orgasms, insufficient lubrication and erectile dysfunction (ED). It could be deduced from certain cases that the basic aetiologies leading to these sexual functional disorders were due to a number of different reasons. Apart from the cases of mixed aetiologies, vascular (arterial, venous), psychogenic, neurogenic, medicamentous-induced and cavernous sexual functional disorders are also differentiated.

[003] Taking into consideration the nature of the underlying aetiologies, causal therapy of the sexual functional disorders is undertaken whenever possible. Up till now this method of therapy has only proved successful in the rare cases (e.g. by psychotherapy, hormone treatment, a change-over of medication) so that the main methods of therapy still remain unspecific.

[004] There are many different methods of therapy available for males with ED compared to those available for females with sexual functional disorders. These include oral, topical, intracavernous, intraurethral and also a combination of drugs. These methods do not constitute a causal therapy, rather the aim is to achieve a direct or indirect relaxation (flaccidity) of the corpus cavernosum smooth musculature and the penile arteries. Together with an increase of blood circulation, penile erection is achieved. Furthermore, the vacuum pump, arterial shunt procedure, venous closure operations and penile prosthesis implantations are also methods used for therapy. Until the introduction of sildenafil (VIAGRA®), the most widely used form of therapy involved the administration of intracavernous vasoactive substances. At the present time, sildenafil is used

as the so-called „first line therapy" providing there are no known contraindications. The oral phosphodiesterase type 5 inhibitor (PDE5) does not provide a basis for causal therapy. With the inhibition of PDE5, hydrolysis of cyclic guanosinmonophosphate (cGMP) of an intracellular second messenger is prohibited, resulting in relaxation of the corpus cavernosum smooth musculature. This effective mechanism is assumed beneficial for the increase of lubrication in women, however, recent studies have yet to prove its effectivity.

Summary of the Invention

[005] The aim of this innovative breakthrough was to present a new therapy for both males and females suffering from sexual functional disorders.

[006] Surprisingly, it has been shown that the growth hormone (hGH) plays an essential role in sexual stimulation, as an enormous unexpected increase of this hormone was seen to be present at the onset of sexual stimulation.

[007] The focal point of this breakthrough is therefore the use of hGH for the manufacture of medicaments for the treatment of sexual functional disorders in both males and females with e.g. lack or loss of libido, problems relating to orgasms, insufficient lubrication and erectile dysfunction and for the therapy of the aforesaid functional disorders.

[008] Accordingly, the present invention is a method of treating female and male sexual functional disorders that includes administering an effective amount of growth hormone. The sexual functional disorder is manifested by a lack or loss of libido, problems relating to orgasms, insufficient lubrication, or erectile dysfunction; there is an insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists. A further aspect is the use of hGH for the therapy of functional disorders in synergic combination with effective substances which result in GH stimulation, induce a GH analogous effect or promote IGF-I release.

Brief Description of the Drawings

[010] **Figure** 1 shows the average values and standard deviations of the growth hormone (hGH) concentrations (ng/ml) in cavernous and peripheral blood samples taken from 35 healthy probands during the four different phases of the penile erectile tissue (flaccidity, tumescence, rigidity and detumescence).

[011] **Figure 2** shows the average values and standard deviations of the growth hormone (hGH) concentrations (ng/ml) in the cavernous and peripheral blood samples during the three different penile phases (flaccidity, tumescence and detumescence) in 36 patients with erectile dysfunction. Rigidity was not achieved due to disorder of patient. The axis scale was selected as in Figure 1 in order to demonstrate clearly the difference ($P<0.05$).

[012] **Figure 3** shows the average values and standard deviations of the dose-dependent decrease in relaxation of 12 human corpus cavernosum strips after application of recombinant hGH.

[013] **Figure 4** shows the average values and standard deviations of dose-dependent increase of cyclic guanosinmonophasphate (cGMP) of 3 human corpus cavernosum strips respectively, following incubation with recombinant hGH or sodium nitroprusside (SNP). Incubation with SNP was carried out using a concentration of 0.01 and 1 µMol. For this reason, no value for SNP was achieved with 0.0001 µMol.

Detailed Description of the Invention

[014] In order to gain a better understanding of the physiology of a naturally induced erection and the pathophysiology of erectile dysfunction, a new method of investigation was developed. This involved detection of endogenous human neurotransmitters, neuromodulators and hormones which might have some connection with an erection or its sexual function. These new methods of investigation aim to improve the diagnostics and therapy (application of endogenous substances and causal therapy) for those patients with sexual functional disorders.

[015] Blood was taken simultaneously from the corpus cavernosum (CC, cavernous) and the cubital vein (CV, peripheral) in 35 healthy probands during the phases of flaccidity, tumescence, rigidity and detumescence. Audiovisual and tactile means were then provided to aid sexual stimulation (**Figure 1**). The procedure involving 36 patients with ED was identical to that of the healthy probands with the exception of blood withdrawal during the rigidity phase, (this penile erection phase cannot be achieved in patients with ED) (**Figure 2**). The hGH concentrations were determined with an immunoradiometric assay (IRMA). This form of investigation resulted in several new findings.

[016] The highest increase of hGH concentration was found during tumescence, namely the point in time when sexual stimulation is at its peak. The peripheral and cavernous hGH concentrations showed no significant differences in direct comparison with all penile phases. Peripheral blood withdrawal proved sufficient. When comparing the healthy probands with the patients, there were significant differences with regards to the hGH concentrations, in particular, a significantly reduced increase of the hGH concentration during the tumescence phase.

[017] These data show for the first time the surprising causal connection of hGH formed by the hypophysis with sexual stimulation and the resulting penile erection. The reduced expression of hGH on sexual stimulation in patients is further proof for the significance of this hormone, the lack of which is connected with sexual functional disorders and erectile dysfunction in this study.

[018] By means of extensive in vitro investigations using human corpus cavernosum (CC) tissue as well as the in vivo results described, important indications could be deduced for the possible physiological connections between hGH and penile erection. Organ bath experiments (in vitro method to evaluate the relaxing properties of substances) with human CC were carried out to assess dose-dependent relaxations following application of hGH (**Figure 3**).

[019] Incubation experiments (in vitro method to evaluate the content of cyclic nucleotides in tissues in response to drug exposition, in this case cGMP, after incubation with various substances) with human CC were shown to have dose-dependent higher cGMP concentrations

after application of hGH than was the case after incubation with sodium nitroprusside (SNP), a classic NO donator (**Figure 4**).

[020] Based on our human findings, it can be assumed that hGH plays a decisive role in sexual function (sexual stimulation), in particular, in penile erection. Furthermore, it was shown that the peripheral reaction of hGH induced an increase of cGMP, thereby physiologically forming a link between relaxation of CC with that of the ensuing erection. Due to the anatomical similarities in the structure of the penis and the clitoris and the physiological conformities regarding sexual stimulation (e.g. congestion of the genital organs mediated by neurotransmitter on relaxation of the smooth musculature), the described reaction of hGH in males must also apply to females too, since hGH is produced by the hypophysis in both sexes, therefore the same effect must also be evident in both sexes.

[021] With reference to the effect of hGH, it is already known that hGH does not focus on any particular tissue and that the activity and metabolism (anabolic) is increased in different tissues in both men and women. The growth hormone stimulates, for example, body growth (substitution in insufficient hGH-caused hyposomia) and protein metabolism (possible indication in cachexia, severe burn injuries and also anabolic abuse). Under the influence of hGH, an insulin-like growth factor I (IGF-I) is formed mainly in the liver but also in other tissues. This polypeptide (IGF-I) plays a significant mediating role in the process induced by hGH (Merimee T.J. and Grant M.B.: Growth hormone and its disorders. In: Principles and Practice of Endocrinology and Metabolism. Edited by Becker, K.L., Philadelphia, J.B. Lippincott Company, pp. 125-134, 1990).

[022] The most recent findings in humans show that there is a systemic increase of NO (nitric oxide) and cGMP under a substitution of recombinant produced hGH (r-hGH) in patients with hGH deficiency (Böger R.H. et al.: Nitric oxide may mediate the hemodynamic effects of recombinant growth hormone in patients with acquired growth hormone deficiency. J. Clin. Invest. 98: 2706-2713, 1996). This NO-cGMP path presents a very important positive significance in achieving penile erection (Burnett A.L. et al.: Nitric oxide: a physiologic mediator or penile erection. Science 257: 905, 1993). Likewise, recent findings derived from animal experiments using rats were able to show that an increase of NOS (nitric oxide synthase)-

containing nerves (generating NO) in CC and dorsal penile nerves occurred under substitution of hGH. This took place despite initiation of neurogenic damage some weeks before (Jung G.W. et al.: Growth hormone enhances regeneration of nitric oxide synthase-containing penile nerves after cavernous neurotomy in rats. J. Urol. 160: 1899-1904, 1998). The patent WO98/42361 (Human erectile dysfunction and methods of treatment) stems from these results and describes the indication of hGH therapy for the prevention and treatment of neurogenic erectile dysfunction of different aetiologies (condition following extensive pelvic operations or pelvic trauma, diabetes, alcoholism and aging process).

[023] Our findings on human models show for the first time a positive causal connection between sexual stimulation, increase of hGH and penile erection. The reduced (often totally lacking) increase of hGH in patients with ED emphasizes the importance of this hormone. The in vitro data conclude that the NO-cGMP path is activated by hGH, leading to relaxation of the CC, thus resulting in penile erection.

[024] The appropriate therapy for all patients (both sexes) with sexual functional disorders includes peripheral blood sample to determine the basal hGH concentration. This form of therapy is undertaken independent of the underlying aetiology(ies). Following this, a further blood sample is taken under sexual stimulation (audiovisual, tactile) in order to detect the stimulated hGH concentration. In cases of insufficient or no reaction at all to sexual stimulation (e.g. lubrication, penile erection) and inadequate increase of hGH concentration, a continuous, strictly controlled therapy with hGH should ensue for a certain period of time (e.g. 2 - 6 months).

[025] Suitable pharmaceutical preparations for therapy include solid or liquid forms of administration for oral intake, such as tablets, capsules or emulsions, parenteral forms of administration for injection or non-invasive application or transdermal topical systems, such as plasters, creams, gels, lotions or transdermal films. The administered amount for successful therapy lies between 0.01 and 500 mg per dosage unit; recommended is between 0.1 and 100 mg.

[026] Improvement of therapy outcome can be achieved by administration of a combination of medicaments containing, besides hGH, a synergic combination of substances which lead to GH stimulation, induce a GH analogous effect or promote IGF-I release.

[027] These substances do not have to be combined into one particular medication, but can be administered in separate suitable galenic preparations to be taken at the same time or taken separately according to the specific course of therapy. It is essential that the specialist instructs and informs the patient with regards to the suitable dosage or in which combination the medicaments should be taken, likewise which substance should be administered to ensure the best possible therapy outcome. Furthermore, it is permissible to combine several of the named substances to treat the individual patient accordingly.

[028] The suitable substances to be used as a combination therapy in order to achieve GH stimulation are familiar to the specialist. For example, arginine, alpha 1 and alpha 2-agonists, such as clonidine, norepinephrine or salbutamol, glucagon, pyridostigmine, galanine, GH-releasing hormone, NPY (neuropeptide Y) and dopamine agonists, such as apomorphine, quinpirole or cabergoline.

[029] Suitable substances which induce a GH analogous effect include, for instance, GHRP (growth hormone, releasing hexapeptide, hexareline), GH releasing peptide 1, 2, 6 and non-peptidergic agonists of growth hormone releasing peptide such as MK 0677, EP 51389 (2-methylalanyl-2-methyl-D-tryptophyl-2-methyl-D-tryptophanamide), L 692429 (3-amino-3-methyl-N-[(3R)-2,3,4,5-tetrahydro-2-oxo-1-[[1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepine-3-yl]butanamide], or L 692585 (3-[[(2R)-2hydroxypropyl]amino]-3-methyl-N-[(3R)-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepine-3-yl]-butanamide).

[030] Suitable substances which promote IGF-I release include, for example, cannabinoide such as e.g. HU-210 (3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol) or serotonine receptor agonists such as e.g. 8-OH

DPAT (8-hydroxy-2-dipropylamino)tetraline), or SC 53116 (4-amino-5-chloro-N-[[(1s,7aS)-hexahydro-1H-pyrrolizine-1-yl]methyl]-2-methoxy-benzamide)